ACE2 at the centre of COVID-19 from paucisymptomatic infections to severe pneumonia

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Dear Editor,

We have read with extreme interest the recent article by Favalli et al[1] published in Autoimmunity Reviews and the following correspondence by Caso et al[2].

We agree with both groups that the current knowledge on the pathogenesis of COVID-19-induced pneumonia resembles very closely autoimmune/autoinflammatory syndromes, thus supporting the current attempts to use conventional and biological DMARDs.

However, as correctly highlighted by both groups, there are a number of open questions. For example, as correctly stated by Caso et al. [2],it remains to be established whether genetic predisposition can contribute to the variability of clinical phenotypes, again pointing towards a similarity between COVID-19 and autoimmune/autoinflammatory syndromes.

Another important question is the identification of the triggers responsible for the development of lung damage and hyperinflammation in the late phases of COVID-19.

Here, we focused our attention on ACE2, the receptor used by SARS-CoV-2, exploring the hypothesis that ACE2 could be at the centre of both lung injury and hyperinflammation.

SARS-CoV-2 and lung injury

One of the most peculiar features of COVID-19 is the development of lung injury, potentially leading to Acute Respiratory Distress Syndrome (ARDS) in a proportion of patients [3]. Pneumonia and ARDS typically develop late in the course of infection, between 5 and 10 days from the onset of symptoms [4]. This is similar to the triphasic pattern observed during the SARS epidemic in 2003, caused by a virus of the same family (SARS-CoV-1)[5]. Following an initial phase of viral replication and cytolysis, characterized by fever and flu-like symptoms, there is a second phase with worsening respiratory symptoms and corresponding to the onset of seroconversion, which was found to be associated with reduced viral load [6,7]. Therefore, clinical worsening in this phase cannot be explained by viral replication, but rather by the exuberant host immune response [8]. Finally, up to 1/3 oSARS-CoV-2 is a novel virf the patients progressed to a third phase, characterized by ARDS [9].

The new COVID-19 follows a similar triphasic clinical pattern, although there seem to be a higher percentage of asymptomatic and pauci-symptomatic individuals [10].

Similarly to SARS, lung inflammation in COVID-19 has been compared to the uncontrolled immune activation seen in haemophagocytic lymphohistiocytosis (HLH) [11] or to the cytokine release syndrome observed in cell-mediated cancer treatment [12] and sepsis [13].

In fact, the clinical picture in severe cases of COVID-19 includes signs of immune system activation, such as high levels of CRP, ferritin and IL-6 [14].

However, it has not been clarified whether this is part of the host response to an ongoing uncontrolled viral inflammation. Importantly, continuous viral shedding has been detected in patients with a negative outcome [14]. Nonetheless, we do not know whether progression to ARDS is actually accompanied by active uncontrolled viral replication, since there has been no actual quantification of viral load. In SARS, for example, it was shown that progression to ARDS was clearly uncoupled from viral load [7].

Therefore, the link between viral replication and lung damage in COVID19 remains elusive and the exact mechanisms responsible for the development of lung damage have not been clarified.

Here, we will look into the evidence suggesting that ACE2, in addition to acting as receptor for the virus, could be directly involved in the development of lung damage and hyperinflammation.

ACE2: more than a backdoor for viral entry?

SARS-CoV-2 binds to the Angiotensin Converting Enzyme 2 (ACE2) via its spike protein [15,16]. Interestingly, SARS-CoV-2 was shown to have a higher affinity for ACE2 than SARS-CoV-1, the virus responsible for SARS [17]. Binding to ACE2 allows the virus to invade cells in the oropharyngeal epithelia [18]. In addition to providing an entry door for SARS-CoV-2, ACE2 could be also involved in the pathogenesis of COVID-19, as it has been clearly implicated in the development of acute respiratory distress syndrome [19].

As shown in Figure 1 a, ACE2 acts as a counterregulatory mechanism of angiotensin II production by ACE. The latter is the target of ACE inhibitors, widely used anti-hypertensive medications [20]. Angiotensin II, upon binding angiotensin receptor I (AT2R1), is responsible, among other functions, for vasoconstriction. Accordingly, angiotensin receptor blockers (ARB) are another well-known category of anti-hypertensive medications.

In recent days, because of the possibility that treatment with ACE inhibitors and ARB can increase ACE2 levels, concern has been raised on the safety of these medications in patients with COVID-19. However, such concerns have been disputed by scientific societies [21] and are not corroborated by the current scientific evidence [22,23].

In fact, if anything, ACE2 has been shown to be protective in several models of lung injury, including SARS-CoV-1-mediated lung injury ([24][19]). Indeed, angiotensin II, in addition to its pro-hypertensive features, is able to activate various cells of the immune system [25], including for example macrophages, inducing the production of proinflammatory cytokines such as IL-6 [26], TNFα and other pro-inflammatory cytokines [27] . Accordingly, angiotensin II has been linked to the development of inflammatory lung injury [28]. Therefore, the inactivation of angiotensin II by ACE2 can explain its protective effects [24].

For the same reasons, the interaction of SARS-CoV-2 with ACE2 can explain many aspects of COVID-19 pathogenesis [29].

As shown in Figure 1 b, when the virus interacts with ACE2 to gain entry into the cells, the downregulation of ACE2 – either direct because of viral binding or indirect because of cell lysis - will remove the brakes from angiotensin II, which in turn can induce the local activation of immune cells. In the lungs, the targeting and destruction of ACE2+ cells per se could explain most of the catastrophic consequences of COVID-19. In fact, when investigating ACE2 expression at single cell level, it was found that ACE2 is expressed by alveolar type II (AT2) cells. AT2 comprise only 5% of the alveoli but produce the surfactant, a factor essential to maintain lung elasticity [30], and, most importantly, act as progenitors for AT1 cells, the latter covering 95% of the alveoli and responsible for gas exchange. In other words, AT2 cells can be considered as alveolar stem cells [31]. Thus, COVID-19 targets and kills the lungs regenerative pool. Depletion of AT2 cells and correspondent surfactant deficit have been previously shown to be associated with incomplete repair of injured alveolar epithelium and fibrotic obliteration [32], thus could also explain the development of lung injury in COVID-19.

Interestingly, a further connection between ACE2 and pollution can be proposed. In fact, an association with quality of air and SARS case fatality has been reported in China [33]. In support of an additional link with ACE2, Lin et al. have shown that ACE2 deficiency attenuates

tissue remodeling and injury repair in response to particulate [34]. Indeed, most of the COVID-19 heavily affected areas at the moment (Wuhan, North of Italy, New York) are known to have high level of particulate or other form of pollution [35–38]. Taken together, these data would suggest that quality of air in these areas could exacerbate an already compromised clinical picture.

Overall, taking into account the above evidence, it is possible to hypothesize a scenario as depicted in Figure 2. SARS-CoV-2 infects ACE2-positive cells in the oral mucosa and lungs, including ACE2+ AT2 cells in the alveoli. In young individuals, higher levels of ACE2 [39] and ACE2+ cells, higher regenerative capacity and a strong immune response lead to an effective viral clearance with little or no symptoms. In older subjects, possibly with lower ACE2 levels, or in the presence of comorbidities that can affect the angiotensin system, such as hypertension [40], or impair the immune response, such as diabetes, the lack of viral clearance and the sustained damage to ACE2+ AT2 cells goes beyond the reparative capacity [41], causing lung inflammation, with a high risk of precipitating into ARDS because of an uncontrolled inflammatory response. This is particularly true during seroconversion, at around 7 to 14 days from the start of viral replication. At this time, when macrophages and immune cells will be already primed by elevated angiotensin II [25], high affinity IgG bound to the virus can cause additional Fc-mediated activation of macrophages, as previously demonstrated for SARS [42].

This working hypothesis, although needing further investigation, would suggest a partial change in the current approach to the management of COVID-19, particularly in terms of applying the right therapeutics at the right time. Accordingly, the presence of a “window of opportunity” for the use of anti-rheumatic drugs in COVID-19 has been recently proposed [43]. For example, the use of antivirals or neutralizing antibodies is probably wrongly timed in the late pneumonia/ARDS phase, when most of the damage seems to be independent from viral replication. Therapies aiming at targeting ACE2 with blocking agents may be equally detrimental, with the risk of worsening an already precarious situation. Finally, the use of immunomodulatory drugs, albeit potentially effective when targeting key mediators involved in ARDS, will target the final links in a much more complex chain of events, with a high risk of being ineffective unless applied at the right time. On the other hand, therapies to boost ACE2 activity or the lung regenerative capacity could be particularly promising for the treatment of COVID-19 [44], as previously described for SARS [45].

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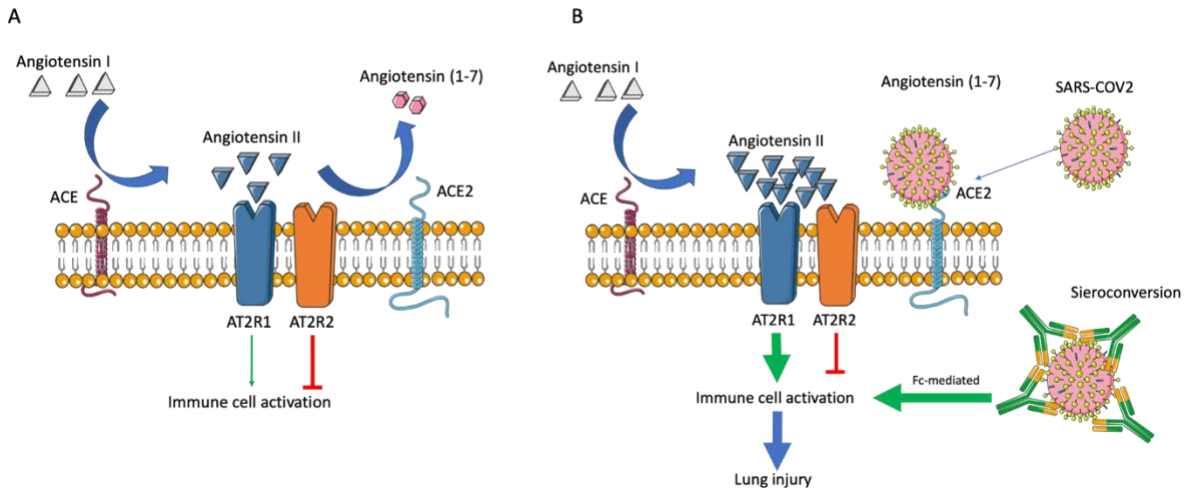
Figure 1


A
Angiotensin I
Angiotensin (1-7)
Angiotensin II
ACE
ACE2
AT2R1
AT2R2
Immune cell activation
B
Angiotensin I
Angiotensin (1-7)
SARS-COV2
Angiotensin II
ACE
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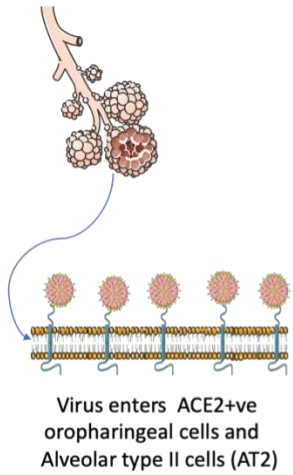
Sieroconversion
AT2R1
AT2R2
Fc-mediated
Immune cell activation
Lung injury

Figure 2

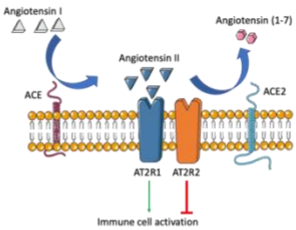


Virus enters ACE2+ve oropharingeal cells and Alveolar type II cells (AT2)

YOUNG

ELDERLY

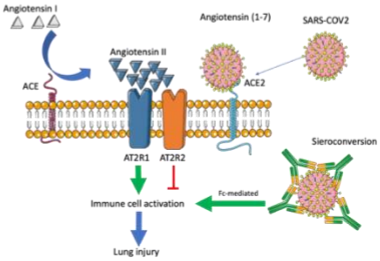
Effective immune response → **virus is cleared**



No functional deficit of ACE2/ AT2 cells

little/no symptoms

Incomplete immune response (age-related) or comorbidities → **Incomplete viral clearance**



ACE2 deficit & destruction of AT2 cells

Lung hyperinflammation & risk of ARDS